REMARKS

Claims 1-12 and 26 were previously cancelled without prejudice. Claims 13-25 are currently pending.

Priority

The Examiner states that the filing date of the instant claims is deemed to be the filing date of PCT/NL03/00254, filed April 4, 2003. See Office Action pages 2-3. The specification has been amended to reflect the correct priority information. Withdrawal of the rejection is respectfully requested.

Priority Claim

The Examiner indicates that the application lacks a priority claim. See Office Action page 4. The specification has been amended to reflect the correct priority information. Withdrawal of the rejection is respectfully requested.

Title of the Invention

The Examiner states that the title of the invention is not descriptive. See Office Action page 4. The title of the invention has been amended. Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. §102(b)

Claims 13-25 are rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Publication 2004/0235074 to Siegall *et al.* (hereinafter referred to as "Siegall"). It is the Examiner's position that Siegall teaches each and every feature of the claimed invention.

The Examiner acknowledges that the Siegall reference does not teach tumor-specific antigens, but alleges that such would be inherent in view of the malignancies set forth in Table 1 on pages 12-13 of the reference. The Examiner also acknowledges that the Siegall reference is silent about the induction of "systemic T cell immunity against an antigen of the tumor... wherein the treatment does not comprise immunization with an antigen of the tumor", per se. See Office Action dated September 10, 2007. However, the

Examiner asserts that it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. The Examiner further asserts that the fact that Applicants may have discovered yet another beneficial effect from the method set forth in the cited references does not mean that Applicants are entitled to receive a patent on that method. See Office Action dated September 10, 2007.

Applicants respectfully traverse the rejection. To support a rejection under Section 102, an Examiner must show that each and every element recited in the claimed invention is taught by a single reference. MPEP §2131. As admitted in the Office Action, Siegall does not expressly teach tumor-specific antigens.

As previously stated, Siegall shows that the use of a specific anti-CD40 antibody seems to induce B cell proliferation *in vitro* in peripheral B cells expressing CD40 (example 7.2.2). However, this example only shows that this specific antibody is able to stimulate B cells *in vitro*.

Siegall further shows that growth reduction of a human tumor is induced in a SCID mouse model using the same human anti-CD40 antibody (example 8). One having ordinary skill in the art is aware that an SCID mouse does not have any T and B cells. Since the anti-CD40 antibody used is a human antibody, it can only induce a growth reduction of the tumor by binding a human CD40 molecule expressed on the tumor itself. Therefore, this experiment shown in Siegall does not demonstrate any *in vivo* activation of T or B cells to exert an anti-tumor effect. Accordingly, Siegall fails to disclose that a systemic T cell immunity can be induced *in vivo* by an anti-CD40 antibody to exert an anti-tumor, let alone an anti-infectious effect.

The Examiner contends that Applicants' arguments focus only on the induction of B-cell proliferation and treatment in an SCID mouse while ignoring the teachings of Siegall in regards to the treatment of cancer and immune disorders.

Although Siegall may broadly suggest the use of anti-CD40 for treating cancer, a person of skill in the art would not consider Siegall an enabling disclosure for the subject matter of the present invention (*i.e.*, the use of agonistic anti-CD40 antibodies for cancer treatment). The experimental data presented by Siegall, as described above, shows an

absence of *in vivo* activation of T or B cells. As stated by the Examiner in the Office Action dated September 10, 2007, Siegall does not teach tumor-specific antigens. A person of ordinary skill in the art, by merely reading a table containing a list of malignancies and disorders, would be unable to make and/or use Applicants' present invention, specifically, the "induction of systemic T cell immunity against an antigen of the tumor or infectious agent" by the administration of the antibody, as required by independent claim 13. Siegall therefore does not disclose each and every element of the present claims.

For these reasons, Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. §103(a)

Claims 13-25 are rejected under 35 U.S.C. §103(a) as being obvious over the teachings of Siegall in view of Melief *et al.* (WO 99/61065; referred to as "Melief"). The Examiner states that Siegall teaches methods of treating cancer through the use of angonistic anti-CD40 antibodies to augment immune responses or the immune system. See Office Action, dated September 10, 2007, page 12. The Examiner again states that Siegall does not teach tumor specific antigens per se but that this limitation would be inherent from Table 1 on pages 12-13. See Office Action dated September 10, 2007. The Examiner also states that although Siegall does not teach the known applicability of using deimmunised and human antibodies as the therapeutic antibodies, or the administration of the antibodies intratumorally, these deficiencies are cured by Melief. See Office Action dated September 10, 2007. The Examiner then concludes that because the goal of the prior art was to treat patients afflicted with tumors with agents that can enhance the immune system or with agents that can treat the tumors, it would have been routine to the ordinary artisan and therefore obvious to design such methods to effectively treat the tumor in the subject. See Office Action at page 9. Applicants respectfully traverse the rejection.

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness. If the Examiner does not satisfy this burden, then the Applicant is not obligated to submit evidence of non-obviousness. See MPEP §2142 at 2100-133 (8th ed., incorporating Revision No. 5, August 2006). The recently revised Examiner guidelines for

assessing obviousness set forth detailed requirements based on asserted rationales for obviousness. The Rationales To Support Rejections Under 35 U.S.C. §103 provide the following possible rationales:

> (A) Combining prior art elements according to known methods to yield predictable results;
>
> (B) Simple substitution of one known element for another to obtain predictable results;
>
> (C) Use of known technique to improve similar devices (methods, or products) in the same way;
>
> (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
>
> (E) "Obvious to try" choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
>
> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; and
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

See MPEP 8th Edition, rev. 6, §2141.

Applicant understands this rejection to conform to rationale G quoted above. The MPEP further sets forth the requirements for an obviousness rejection under this rationale:

> To reject a claim based on [rationale G], Office personnel must resolve the Graham factual inquiries. Then, Office personnel must articulate the following:
>
> (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
>
> (2) a finding that there was reasonable expectation of success; and

> (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.
>
> The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006). **If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.**

See MPEP 8th Edition, rev 6, §2143

The Office Action fails to cite any motivation for the combination of Siegall with Melief. The Office Action also fails to state why such a combination would hypothetically disclose the present invention.

As explained in detail above, Siegall does not contain an enabling disclosure of the present invention. Siegall does not teach to one of ordinary skill in the art the use of agonistic anti-CD40 antibodies for cancer treatment. Given the teachings of Siegall as outlined above, a person of skill in the art would determine that the use of the anti-CD40 antibody would not allow the induction of a systemic T cell response. Because the T cell response would not be induced, a skilled artisan would in fact be discouraged from using such an antibody. Melief does not cure the deficiencies of Siegall. Melief teaches that activation of anti-CD40 antibodies is insufficient to induce systemic T cell response, thus confirming the insufficiencies of Siegall. A combination of the two references teaches that induction of a T cell response requires *both* an activating anti-CD40 antibody *and* a CTL-activating peptide, thus teaching away from the present invention.

Further, the Examiner has agreed that the present invention is novel over Melief, thus admitting that Melief does *not* disclose the use of an anti-CD40 antibody without a CTL-activating peptide.

In addition, the present application teaches an effective method for treating tumors through the induction of a systemic T cell response. Siegall fails to recognize the

importance of systemic T cell induction for tumor treatment. In fact, Siegall teaches only the induction of an *in vitro* B cell response, as explained in detail previously. As outlined above, Melief teaches the use of both a CTL-activating peptide and an anti-CD40 antibody. Thus, a person of skill in the art would have no motivation to use only an anti-CD40 antibody.

The Examiner repeatedly admonished Applicants for concentrating "solely" on the Examples of Siegall (See Office Action page 5, third and fourth paragraph; page 7, eighth and ninth paragraph). However, Applicants respectfully submit that the Examiner appears to focus on a single paragraph of the Siegall specification in concluding that Melief discloses the use of an anti-CD40 antibody without the use of a CTL-activating peptide. It appears that the Examiner is ignoring the clear teaching of Melief in that Melief teaches the use of *both* a CTL-activating peptide and an anti-CD40 antibody.

It appears that the Examiner is of the opinion that Melief does not contain a teaching away, but rather represents a skeptic view of a person of skill in the art in regards to the use of an anti-CD40 antibody as the sole agent in inducing systemic T cell immunity. However, the very case law cited by the Examiner indicates that "general skepticism" is relevant for assessing non-obviousness (see Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 726 (Fed. Cir. 1990); "General skepticism of those in the art—not amounting to teaching away—is also 'relevant and persuasive evidence' of nonobviousness.'"; See Office Action at page 8). Thus, it appears that the Examiner is agreeing with Applicants in the conclusion that the combination of Siegall and Melief teach away from the present invention.

Accordingly, for the reasons set forth above, it is respectfully requested that the rejection of claims 13-25 under 35 U.S.C. §103(a) be withdrawn as the combination of Siegall with Melief fails to render these claims obvious.

CONCLUSION

Based on the foregoing remarks, reconsideration of the rejection and allowance of pending claims 13-25 are respectfully requested.

Respectfully submitted,

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